

## Metformin use and prostate cancer in Caucasian men: results from a population-based case–control study

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### Abstract

**Purpose** Metformin is a commonly used medication for type II diabetes mellitus. Epidemiologic studies have suggested a decreased relative risk of cancer with metformin use, and preclinical studies of prostate cancer (PCa) have shown antitumor activity with metformin. In this study, we explore the relationship between metformin use and PCa risk in a population-based case–control study.

**Methods** Cases were men aged 35–74 years diagnosed with PCa between 2002 and 2005 in King County, Washington. Controls were frequency matched by age and identified by random digit dialing. Use of metformin was determined from in-person questionnaires regarding medical and prescription history. The relationship of metformin use with PCa risk was evaluated using logistic regression. **Results** A total of 1,001 cases of PCa and 942 controls were available for analysis. In Caucasian men, metformin use was more common in controls than in cases (4.7 vs. 2.8%,  $p = 0.04$ ), resulting in a 44% risk reduction for PCa (adjusted OR = 0.56; 95% CI 0.32–1.00). No association was seen in African-American men.

**Conclusion** Metformin use was associated with a borderline significant decrease in the relative risk of PCa in Caucasians. Further study into this relationship is needed to confirm the association and determine the underlying pathways involved.

**Keywords** Prostate cancer · Metformin · Case–control study · Disease risk · Population based

### Introduction

Prostate cancer (PCa) is the most common noncutaneous cancer diagnosed in men, with a 1 in 6 lifetime risk of developing clinically diagnosed PCa [1]. Type II diabetes mellitus (DM) is also a common disease, and some studies have shown a link between PCa and DM [2, 3]. Metformin is a frequently used medication for patients with DM that has received increased attention because of a study from pharmacy and disease databases showing decreased cancer incidence in individuals taking metformin [4]. A second study reported decreased cancer mortality in diabetic patients taking metformin compared to those taking sulfonylureas/insulin [5]. Several potential mechanisms for this antineoplastic action of metformin have been suggested, including AMP-kinase pathway (AMPK) activation [6, 7], p-53 activation [8], downregulation of cyclin D1 [7, 9] and suppression of HER2 oncoprotein expression [6]. These findings are consistent with animal and in vitro studies demonstrating decreased growth of a number of different malignant cell types treated with metformin [6–14], including PCa cell lines [9, 13]. In this study, using a population-based case–control study of PCa, we explore the relationship between metformin use and PCa risk.

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## Methods

### Study participants

The study population consists of participants in a population-based case–control study of PCa. Details of the study participants and data collection have previously been described [15]. Briefly, cases were Caucasian and African-American residents of King County, Washington with histologically confirmed PCa ascertained from the Seattle–Puget Sound SEER cancer registry and diagnosed between 1 January 2002, and 31 December 2005. Of those eligible men identified, 75% ( $n = 1,001$ ) agreed to participate. Male residents of King County, Washington with no history of PCa were identified as a comparison group using random digit telephone dialing. Controls were frequency matched to cases by 5-year age groups and recruited evenly throughout the ascertainment period for cases. During the first step of random digit dialing, complete household census information was obtained for 81% of the 24,106 residential telephone numbers contacted. Of eligible men who were identified and met the study eligibility criteria, 63% ( $n = 942$ ) completed the study interview.

### Data collection

Subjects completed in-person interviews conducted by trained interviewers who collected information about demographic and lifestyle factors, medical, medication use and family history, and PSA and DRE screening in the previous 5 years. Participants were asked whether prior to reference date (date of diagnosis for cases and a randomly preassigned date for controls that approximated the distribution of diagnosis dates of cases) a doctor ever told them they had had diabetes; and if so, when they were first diagnosed and what prescription medications they had used. Up to six different medications could be listed. For this study, the following drug names for metformin were reported: metformin, Fortamet, Glucophage, Glucophage XR, Glumetza, Riomet and Metaglip. The other classes of diabetic medications were also collected: sulfonyureas (Amaryl, Glucotrol, Diabeta, Diabinese, Glipizide, Metaglip), thiazolidinediones (Actos, Avandia, Rezulin, Rosiglitazone), Insulin (Insulin, Humulin, Lispro, Glargine) and Meglitinides (Starlix).

### Statistical analysis

The relative risk of PCa associated with the different diabetic treatments was calculated by logistic regression. Potential confounders that were included in the multivariate model included age, PSA screening history and family history of PCa. We also adjusted for body mass index

(BMI), statin medication use and aspirin use as these have been associated with an alteration in the risk of PCa and are often observed/taken by diabetic men. Effect modification was also examined and revealed evidence of differing effects of metformin use on PCa risk by race (interaction  $p = 0.03$ ). Results were, therefore, stratified by race. A second model was created where the primary predictor of interest was categorized as follows: no diabetes, diabetes – not taking metformin, diabetes – taking metformin. This was performed to further evaluate whether it was diabetes or metformin use impacting PCa risk. Further, polytomous regression was used to calculate the risk according to disease aggressiveness (controls, less aggressive, more aggressive). Disease aggressiveness was based on a composite variable incorporating Gleason score, stage and PSA, where more aggressive PCa was defined as Gleason 4 + 3 or greater; nonlocalized stage or PSA  $\geq 20$  ng/ml at time of diagnosis. All statistical analyses were conducted using Stata software, Version 8 (Stata Inc., College Station, TX).

## Results

Table 1 lists the distribution of selected characteristics of cases and controls. Table 2 lists the proportions of cases and controls reporting DM and metformin use. The overall frequencies of DM (9.7 and 10.7%) and metformin use (4.0 and 4.8%) were similar between cases and controls, respectively. However, results differed by race. Among Caucasians, DM (7.8 vs. 10.2%,  $p = 0.09$ ) and metformin use (2.8 vs. 4.7%,  $p = 0.04$ ) were less common in cases compared to controls, respectively. There was no difference in the frequency of DM or metformin use between African-American controls and cases, although very limited numbers were available for this analysis. Increasing BMI ( $p < 0.001$ ) was associated with a higher prevalence of metformin use in both cases and controls in both races (data not shown).

In Table 3, the prevalence of ever use of diabetic and other medications are provided for cases and controls. Metformin was the most common medication taken for diabetes. Use of aspirin and statins was common in both groups. In Table 4, the age-adjusted and multivariate ORs and 95% CIs are reported for PCa risk and diabetic treatment in Caucasians. A 39% reduction in the age-adjusted relative risk (OR = 0.61; 95% CI 0.37–1.02) was seen in Caucasian men reporting metformin use, but no association was observed in African-Americans (OR = 1.62; 95% CI 0.53–5.02, data not shown). In the multivariate model (adjusting for other diabetes treatments, statin and aspirin uses, BMI, PSA testing and family history of PCa), there was a 44% reduction in risk of PCa in Caucasians

**Table 1** Selected characteristics of prostate cancer cases and controls

	Cases <i>n</i> (%)	Controls <i>n</i> (%)	<i>p</i> -Value
Total	1001 (100)	942 (100)	
Age at reference date (years)			
35–54	201 (20.1)	209 (22.2)	0.49
55–64	402 (40.2)	361 (38.3)	
65–74	398 (39.8)	372 (39.5)	
Race			
Caucasian	843 (84.2)	844 (89.6)	<0.001
African-American	158 (15.8)	98 (10.4)	
Family history of prostate cancer			
No	775 (77.4)	833 (88.4)	<0.001
Yes	226 (22.6)	109 (11.6)	
PSA screening within the past 5 years			
None	220 (22.0)	240 (25.5)	<0.001
1–2 PSAs	172 (17.2)	168 (17.8)	
≥3 PSAs	546 (54.6)	380 (40.3)	
Unknown	63 (6.3)	154 (16.4)	
BMI			
Normal (<25)	287 (28.7)	259 (27.5)	0.26
Overweight (25–29.9)	492 (49.2)	444 (47.1)	
Obese (≥30)	222 (22.2)	239 (25.4)	
Income			
<\$50,000	322 (33.6)	309 (33.7)	0.96
\$50,000+	637 (66.4)	608 (66.3)	
Education			
High school only	196 (19.6)	181 (19.2)	0.76
Some college/vocational	241 (24.1)	210 (22.3)	
Bachelors degree	262 (26.2)	261 (27.7)	
Graduate degree	301 (30.7)	289 (30.7)	

(OR = 0.56, 95% CI 0.32–1.00). In the second model where non-metformin treatments of diabetes were grouped together, the presence of diabetes without metformin use was not associated with a decrease in PCa risk in the multivariate model (OR = 0.95, 95% CI 0.60–1.49), whereas there was a decreased risk in those with diabetes taking metformin, with a similar OR compared to that for metformin in the 1st model (OR = 0.66, 95% CI 0.39–

1.11). More aggressive PCa features were present in 31.5% (*n* = 315) of cases and the remainder had less aggressive PCa (*n* = 686). In the polytomous model, compared to controls, we found a reduction in risk of PCa associated with metformin use for both less aggressive PCa (OR = 0.63, 95% CI 0.33–1.19) and more aggressive PCa (OR = 0.43, 95% CI 0.17–1.09). The risk estimates for the PCa aggressiveness categories were not significantly different (*p* = 0.45).

## Discussion

In this population-based case–control study, we observed a borderline significant reduction in the relative risk of PCa in Caucasian men taking the antidiabetic drug metformin. These results are consistent with findings from earlier epidemiologic studies and with preclinical studies demonstrating antitumor activity of metformin.

Metformin is an oral anti-hyperglycemic medication used in the management of type II DM that functions primarily through improved insulin sensitivity and decreased hepatic gluconeogenesis [16]. It is the most common drug used for treatment of type II DM and has been available in the United States since 1995 [17]. Metformin has a number of additional cellular activities that have potential antineoplastic activity including AMP-kinase pathway activation [6, 7], p-53 activation [8], downregulation of cyclin D1 [7, 9], and suppression of HER2 oncoprotein expression [6].

Recently, a Scottish case–control study found a reduced risk of overall cancer in diabetic patients taking metformin [5]. In that study, a diabetic clinical information system was linked to a prescription database and those with any vs. no metformin exposure had a 23% lower OR for cancer of any type (OR = 0.77; 95% CI 0.64–0.92). The strongest risk reduction was observed in those with the longest durations of metformin use. An additional population-based study in Saskatchewan linked a prescription database with a cancer registry and vital statistics database [4]. Diabetic patients taking metformin or a sulfonylurea were identified and followed for cancer-specific mortality.

**Table 2** Distribution of diabetes mellitus and metformin use in cases and controls, by race

	All men			Caucasians			African-Americans		
	Cases	Controls	<i>p</i> -Value	Cases	Controls	<i>p</i> -Value	Cases	Controls	<i>p</i> -Value
Diabetes mellitus									
No	904 (90.3)	841 (89.3)	0.45	777 (92.2)	758 (89.8)	0.09	127 (80.4)	83 (84.7)	0.38
Yes	97 (9.7)	101 (10.7)		66 (7.8)	86 (10.2)		31 (19.6)	15 (15.3)	
Metformin use									
No	962 (96.1)	897 (95.2)	0.34	819 (97.2)	804 (95.3)	0.04	143 (90.5)	93 (94.9)	0.20
Yes	40 (4.0)	45 (4.8)		24 (2.8)	40 (4.7)		15 (9.5)	5 (5.1)	

**Table 3** Even use of diabetic and other medications by prostate cancer cases and controls

	Cases <i>n</i> (%)	Controls <i>n</i> (%)
Diabetes medication usage		
Metformin	40 (4.0)	45 (4.8)
Insulin	24 (2.4)	29 (3.1)
Sulfonylureas	14 (1.4)	11 (1.5)
Thiazolidinediones	17 (1.7)	14 (1.5)
Meglitinides	1 (0.1)	1 (0.1)
Other medication usage		
Aspirin	484 (48.4)	486 (51.6)
Statins	289 (28.9)	265 (28.1)

Patients taking sulfonylureas had an increased risk of cancer-specific mortality compared to those taking metformin (hazard ratio = 1.3; 95% CI 1.1–1.6). Few studies have looked specifically at PCa risk and diabetes treatment. In a large Finnish population-based registry study, a decrease in PCa risk was observed for the use of any antidiabetic drug [18]. This study found that duration of treatment was inversely related to PCa risk, suggesting that it is diabetes rather than any specific medication that decreases the risk of PCa. However, the investigators were unable to adjust for BMI, family history of PCa or PSA screening history. Further, the Finnish population is 98% Caucasian, so the differences we observed in race cannot be compared. A multi-ethnic study found an association between PCa and DM in European-Americans (RR = 0.65, 95% CI 0.50–0.84,  $p = 0.001$ ) but not in African-Americans (RR = 0.89, 95% CI 0.77–1.03,  $p = 0.13$ ) [3]. This was especially true in those with higher Gleason scores >7 [European-Americans (RR = 0.68, 95% CI

0.43–1.07,  $p = 0.09$ ) and African-Americans RR = 0.98, 95% CI 0.71–1.29,  $p = 0.76$ ]. These results are consistent with our findings of effect modification of metformin use by race. Why diabetes and/or treatment effects on PCa risk would differ by race is unknown. African-American men often have a delay in diagnosis of DM and worse glycemic control [19], which may partially explain these findings. These differences may also relate to underlying genetic or environmental exposures and deserve further investigation.

There are several reasons to suspect that metformin may have specific anticarcinogenic properties, as it has shown inhibitory effects in preclinical models of a number of different tumor types, including prostate [9, 13], breast [6, 10, 12], pancreatic [11], lung [14] and colon cancers [8, 13]. In fact, metformin has recently been associated with increased complete response rates in women with breast cancer receiving neoadjuvant chemotherapy [20] and work is underway for Phase III trials of metformin in early stage breast cancer [21]. PCa risk has been associated with hyperinsulinemia [22, 23] and unlike sulfonylureas and exogenous insulin, metformin does not increase insulin levels [16], which may be one mechanism whereby metformin exhibits antitumor activity. Additionally, in PCa cell lines (LnCaP, PC-3, DU145), metformin has been shown to inhibit cyclin D1 expression, blocking the cell cycle in G<sub>0</sub>/G<sub>1</sub> [9]. Metformin has also been shown to activate AMP-activated protein kinase (AMPK) in PC-3 cell lines [13]. AMPK is activated in response to cellular stress leading to an increased AMP/ATP ratio [24]. AMPK has gained attention for its downstream effects of reduced cellular proliferation and protein synthesis [25] along with mTOR inhibition [6, 10]. The precise pathway(s) that may be involved with metformin and its potential antitumor activity has not been defined and may involve more than

**Table 4** Age-adjusted and multivariate risk of prostate cancer among Caucasians by diabetes treatment

	Age-adjusted model		Multivariate model <sup>a</sup>	
	OR	95% CI	OR	95% CI
Model 1				
Diabetes treatment				
Metformin	0.61	0.37–1.02	0.56	0.32–1.00
Insulin	0.76	0.39–1.47	0.95	0.47–1.92
Sulfonylureas	1.28	0.58–2.84	1.79	0.74–4.33
Thiazolidinediones	1.08	0.52–2.25	1.34	0.58–3.13
Diet and exercise only	0.92	0.51–1.65	0.97	0.53–1.78
Model 2				
No diabetes	1.00	Referent	1.00	Referent
Diabetes, not taking metformin	0.87	0.56–1.34	0.95	0.60–1.49
Diabetes, taking metformin	0.61	0.37–1.02	0.66	0.39–1.11

<sup>a</sup> Adjusted for age, other diabetic treatments, aspirin and NSAID usage, bmi, psa tests in preceding 5 years and family history of prostate cancer

one mechanism. Although our study does not evaluate any of the specific pathways that may be involved, our results draw attention specifically to PCa risk based on exposure to metformin and support ongoing efforts to explore the link between metformin exposure and PCa.

There are limitations of our study. We cannot assess duration of use of metformin, nor can we distinguish type I from type II DM. However, early onset type I is rare, and only three participants (1 case; 2 controls) reported being diagnosed with DM prior to age 18; exclusion of these men did not change our results. Overall, 10.7% of our population-based controls reported DM, which is similar to the 11% prevalence in the general US population of men over the age of 20 years [26]. We also rely on participant-reported use of medications rather than pharmacy records. In a separate analysis of a subset of this study population that was designed to validate use of statin medications, there was 87% agreement between self-reported use and computerized pharmacy records [15]. There are data showing a reduced risk of PCa in diabetic men [2, 3], such that our findings of a reduced risk in men taking metformin may be due to an independent aspect of diabetes. Further, DM may be associated with lower PSA levels [27], which could introduce detection bias. Additionally, our finding may be due to chance and should be replicated in a larger study. Despite these limitations, these findings are in support of the growing evidence from preclinical and epidemiological data supporting the potential antitumor activity of metformin. These results indicate that additional studies are warranted to evaluate the potential metformin-PCa association.

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